GELL AND COOMBS

INTRODUCTION

- Defense against microbes is mediated by:
  - Innate immunity
    - Early reactions
    - Also called natural or native immunity
  - Adaptive immunity
    - Late responses
    - High specificity
    - Memory

INTRODUCTION

- Adaptive immunity
  - Is important for host defense against microbial infections
  - Can cause tissue injury and disease
- Hypersensitivity diseases
  - Disorders caused by immune responses

INTRODUCTION

- A common cause of hypersensitivity disease is failure of self-tolerance
  - Property of the immune system that ensures that individuals do not respond to their own antigens
- Disorders caused by failure of self-tolerance are called autoimmune diseases

INTRODUCTION

- Hypersensitivity diseases may also result from uncontrolled or excessive responses against foreign antigens
  - Microbes
  - Noninfectious environmental antigens

GELL AND COOMBS

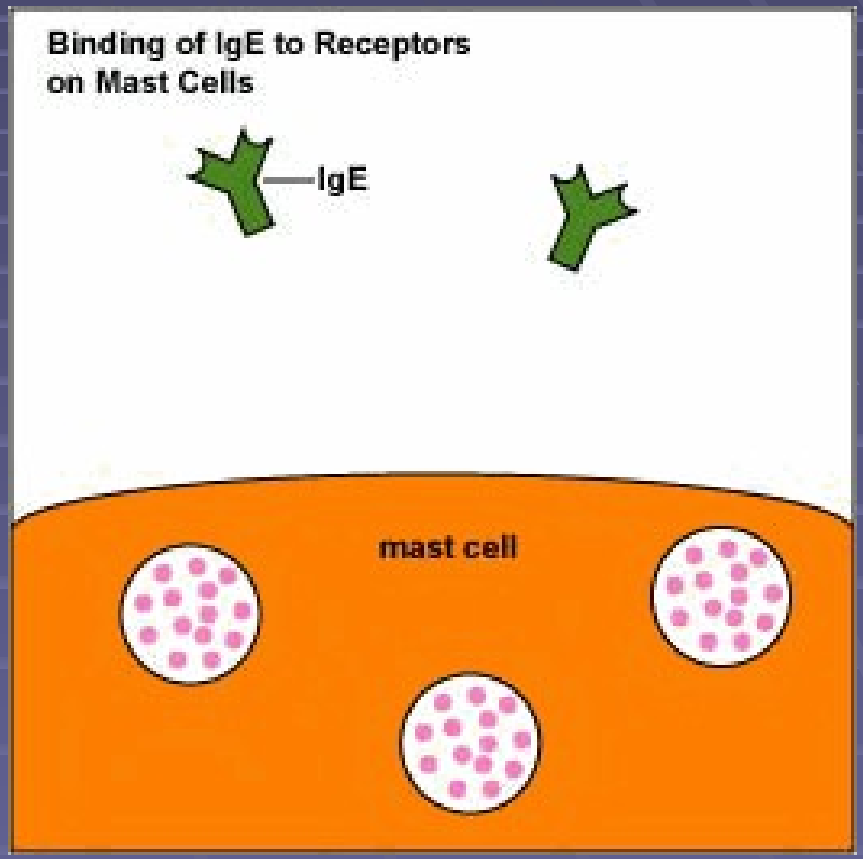
- **Von Pirquet**
  - Coined the term “Allergy” in 1906
    - Derived from Greek word “allos” meaning changed or altered state and “ergon” meaning reaction
    - Reaction may be host protective or injurious

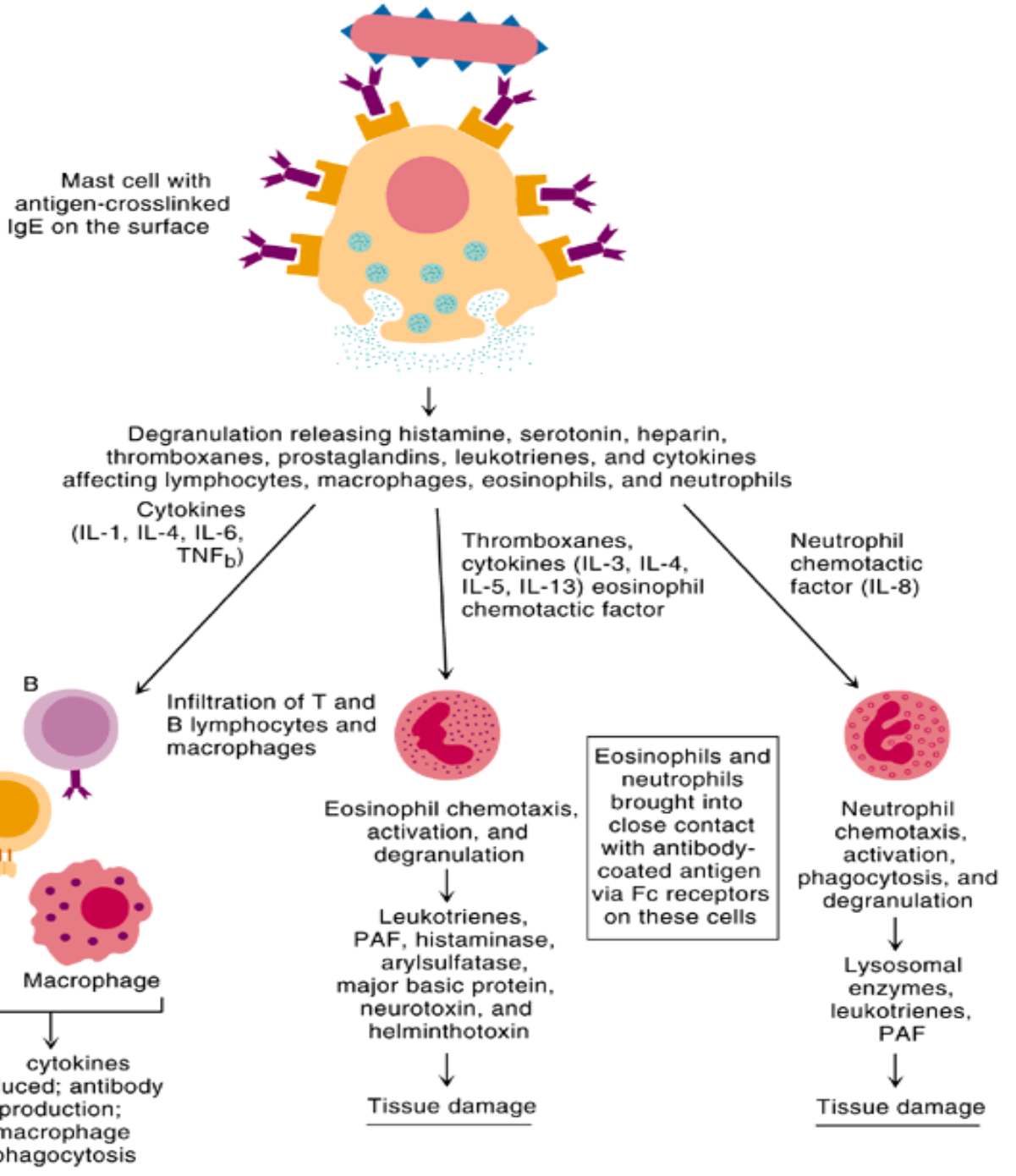
HYPERSENSITIVITY CLASSIFICATIONS

- **Gell and Coombs**
  - Developed classification of hypersensitivity reactions (1963)
    - Type I Hypersensitivity- IgE mediated
    - Type II Hypersensitivity- Antibody mediated
    - Type III Hypersensitivity- Immune complex
    - Type IV Hypersensitivity- Cell mediated

TYPE I HYPERSENSITIVITY

- All immediate hypersensitivity reactions share common features
  - Exposure to antigen
  - Activation of Th-2 cells
  - Stimulation of IgE class switching on B cells
  - Production of IgE
  - Binding of IgE on mast cells (sensitization)
  - Repeated exposure to allergen
  - Activation of mast cell: release of mediators




Mast cell with antigen-crosslinked IgE on the surface
Degranulation releasing histamine, serotonin, heparin, thromboxanes, prostaglandins, leukotrienes, and cytokines affecting lymphocytes, macrophages, eosinophils, and neutrophils
Cytokines (IL-1, IL-4, IL-6, TNFb)
Thromboxanes, cytokines (IL-3, IL-4, IL-5, IL-13) eosinophil chemotactic factor
Neutrophil chemotactic factor (IL-8)
B
T
Infiltration of T and B lymphocytes and macrophages
Macrophage
TH2 cytokines produced; antibody production; macrophage phagocytosis
Eosinophil chemotaxis, activation, and degranulation
Leukotrienes, PAF, histaminase, arylsulfatase, major basic protein, neurotoxin, and helminthotoxin
Tissue damage
Eosinophils and neutrophils brought into close contact with antibody-coated antigen via Fc receptors on these cells
Neutrophil chemotaxis, activation, phagocytosis, and degranulation
Lysosomal enzymes, leukotrienes, PAF
Tissue damage

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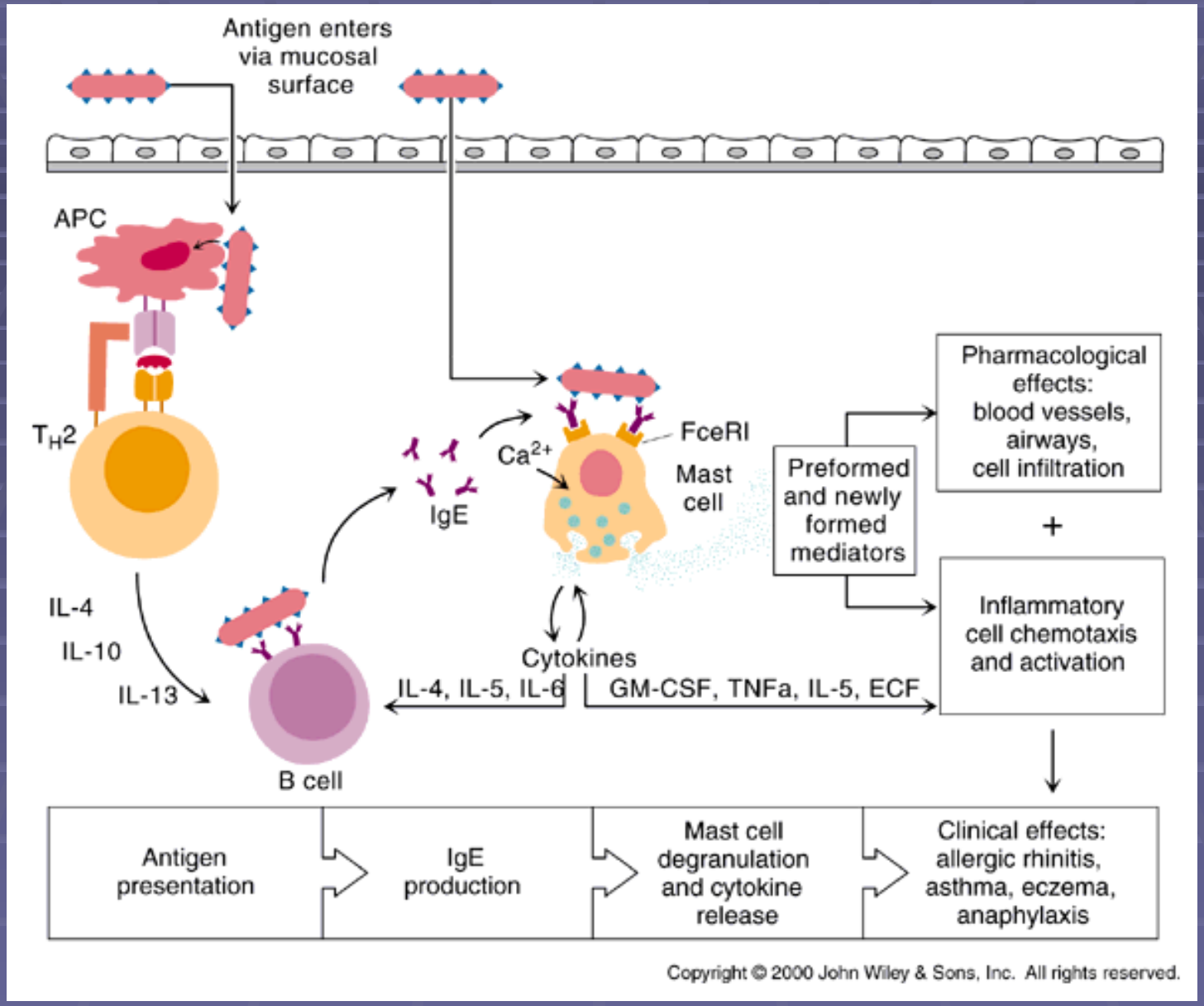

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TYPE I HYPERSENSITIVITY

- Clinical Diseases
  - Anaphylaxis
  - Asthma
  - Allergic Rhinitis
  - Atopic Dermatitis
  - Food Allergy

TYPE I HYPERSENSITIVITY

- Mast cells are present in all connective tissues and under all epithelia
  - Many sites for clinical symptoms
    - General
      - Fear of impending doom
    - Skin
      - Erythema, flushing, angioedema, urticaria
    - Eyes
      - Pruritus, lacrimation, edema
    - Nose
      - Pruritus, congestion, sneezing, rhinorrhea
    - Mouth
      - Metallic taste, angioedema of lips and/or tongue

TYPE I HYPERSENSITIVTY

- Clinical Sites Continued
  - Upper airway
    - Stridor, hoarseness, dysphonia, laryngeal edema OBSTRUCTION DEATH
  - Lower airway
    - Dyspnea, wheezing, cough, chest tightness
  - Cardiovascular
    - Tachycardia, hypotension, arrhythmias, lightheadedness, shock
- Type I Hypersensitivity detection
  - Skin testing
  - RAST testing

DISEASES CAUSED BY ANTIBODIES

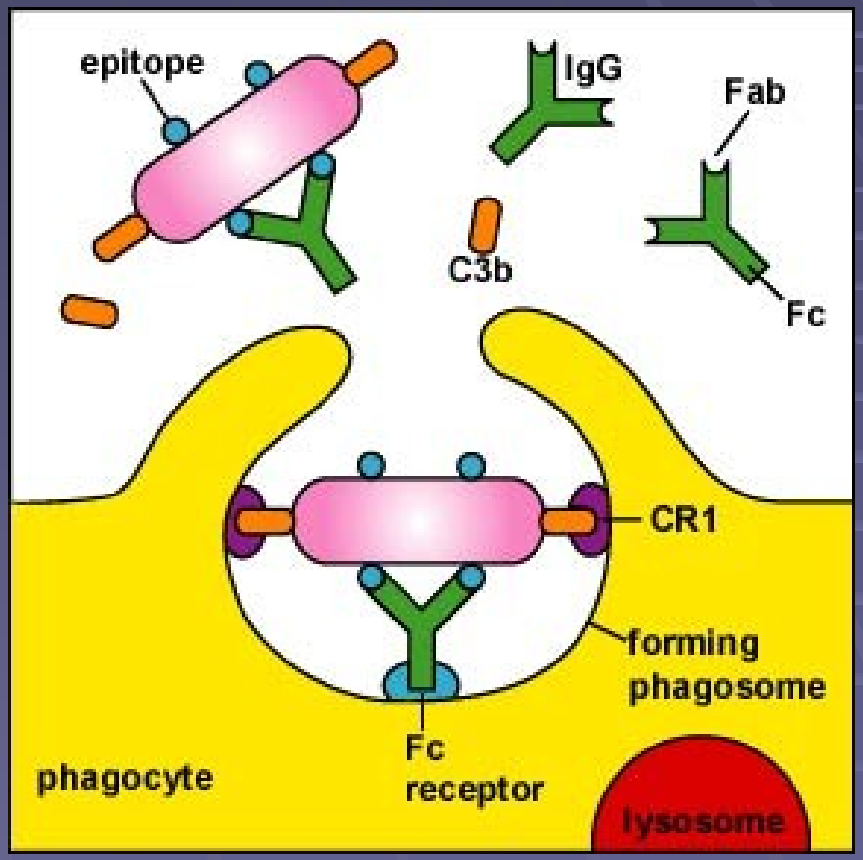
- Immune responses are the same for both self and non-self antigens
- Antibody-mediated diseases are produced by responding to antigens on cells/tissue or by antigen-antibody complex formation and deposition
  - Type II Reactions
    - Antigen-antibody mediated
  - Type III Reactions
    - Antigen-antibody mediated immune complexes

DISEASES CAUSED BY ANTIBODIES (Type II)

- **Diseases Caused by Antibodies Against Fixed Cell and Tissue Antigens**
  - Reaction only at specific location of antigen
  - Not systemic
  - Mechanisms responsible for disease:
    - Opsonization and phagocytosis
    - Complement and Fc receptor mediated inflammation
    - Abnormal physiologic responses without cell/tissue injury

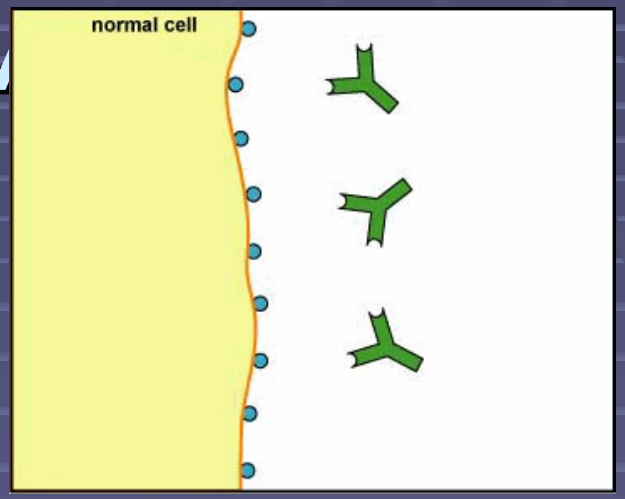
OPSONIZATION AND PHAGOCYTOSIS (Type II)

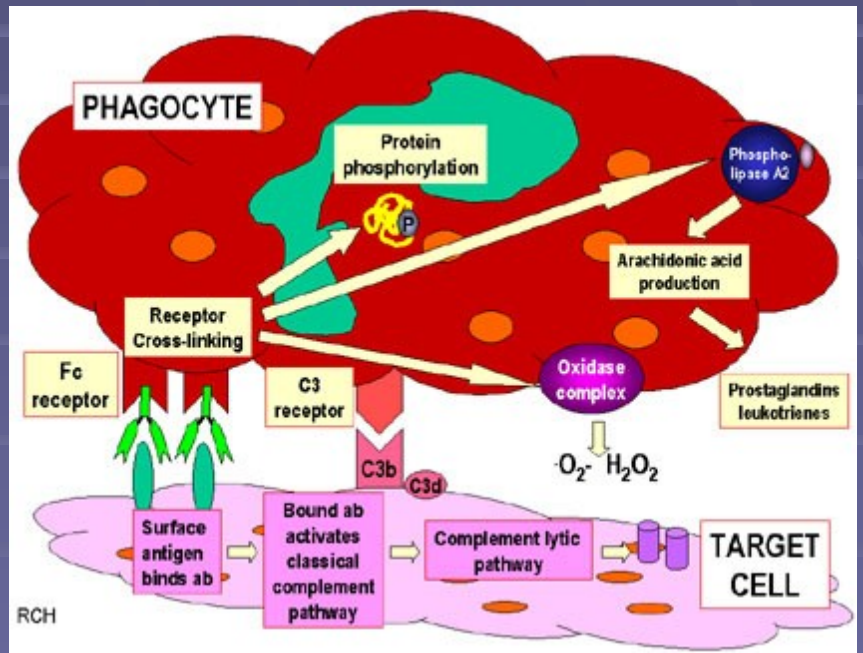
- Antigen recognized by antibody
- Phagocytes recognize Fc portion of antibody
- Cell phagocytosed
- May occur through complement recognition
- Primary mechanism involved in hemolytic anemia



COMPLEMENT AND Fc RECEPTOR MEDIATED INFLAMM

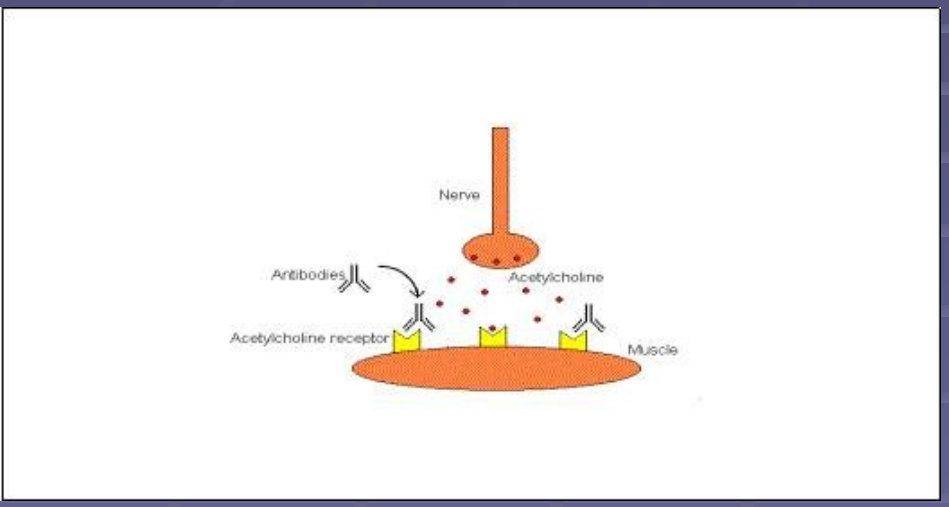
- Antibodies recognize antigen
- Complement activation
- Neutrophils and macrophages recruited
- Recruited cells bind to antibody or complement that has been activated
- Recruited cells release products that cause tissue injury
- Primary mechanism of antibody mediated glomerulonephritis

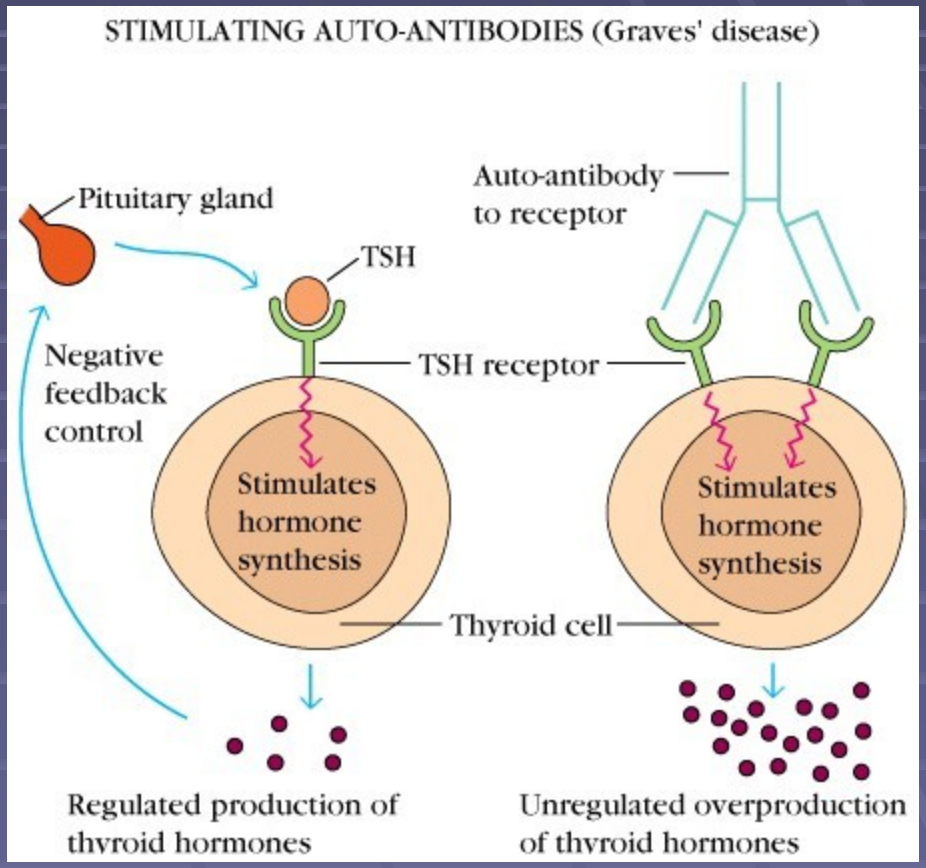




ABNORMAL PHYSIOLOGIC RESPONSE

- Antibody recognizes receptor
  - Stimulation





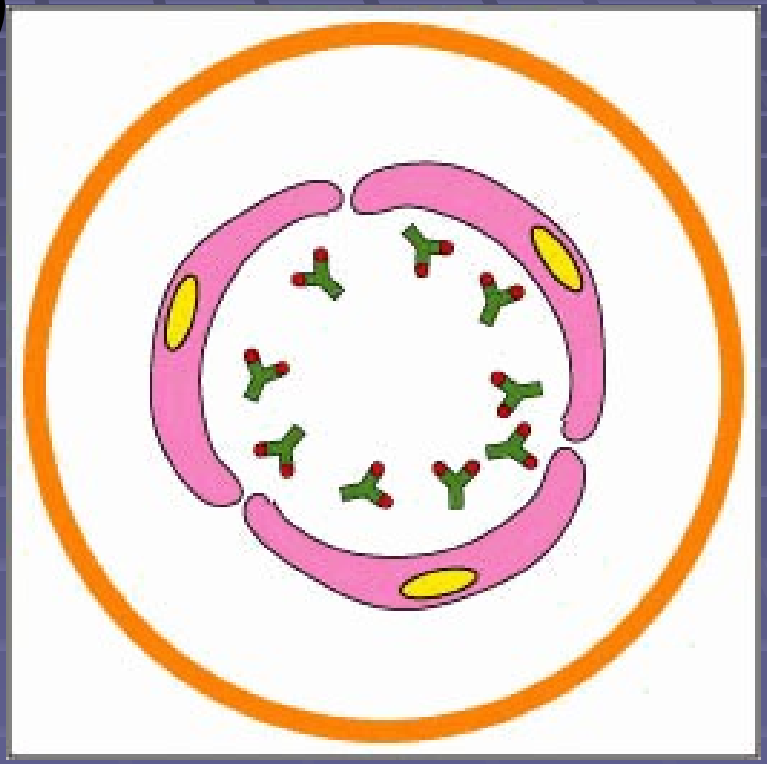
IMMUNE COMPLEX MEDIATED DISEASE (Type III)

- **First suspected in 1911**
  - Clemens von Pirquet
  - Diphtheria infections were treated with serum from immunized horses
  - Von Pirquet noted fever, rash and joint inflammation in patients receiving antitoxin-containing horse serum
    - Occurred after horse serum without anti-toxin
    - Symptoms appeared at least a week after the first injection and more rapidly with each repeated injection
  - Von Pirquet suggested that the host made antibodies to horse serum proteins
    - Disease was secondary to antibodies or immune complexes
    - He called this serum disease

- Immune complexes may be composed of either foreign or self antigens bound to antibodies
- Pathology occurs at site of deposition
  - Not determined by the cellular source of antigen

IMMUNE COMPLEX MEDIATED DISEASE (Type III)

- Produced during normal responses
  - Disease with excessive amounts or if not cleared
- Small complexes tend to be deposited whereas large complexes often are phagocytosed
- Complexes containing cationic antigens bind well to negatively charged components on the basement membranes of blood vessels and glomeruli
- Deposition of complexes leads to complement and Fc receptor mediated inflammation and injury to the vessels and adjacent tissues
- SLE prototypic immune complex disease

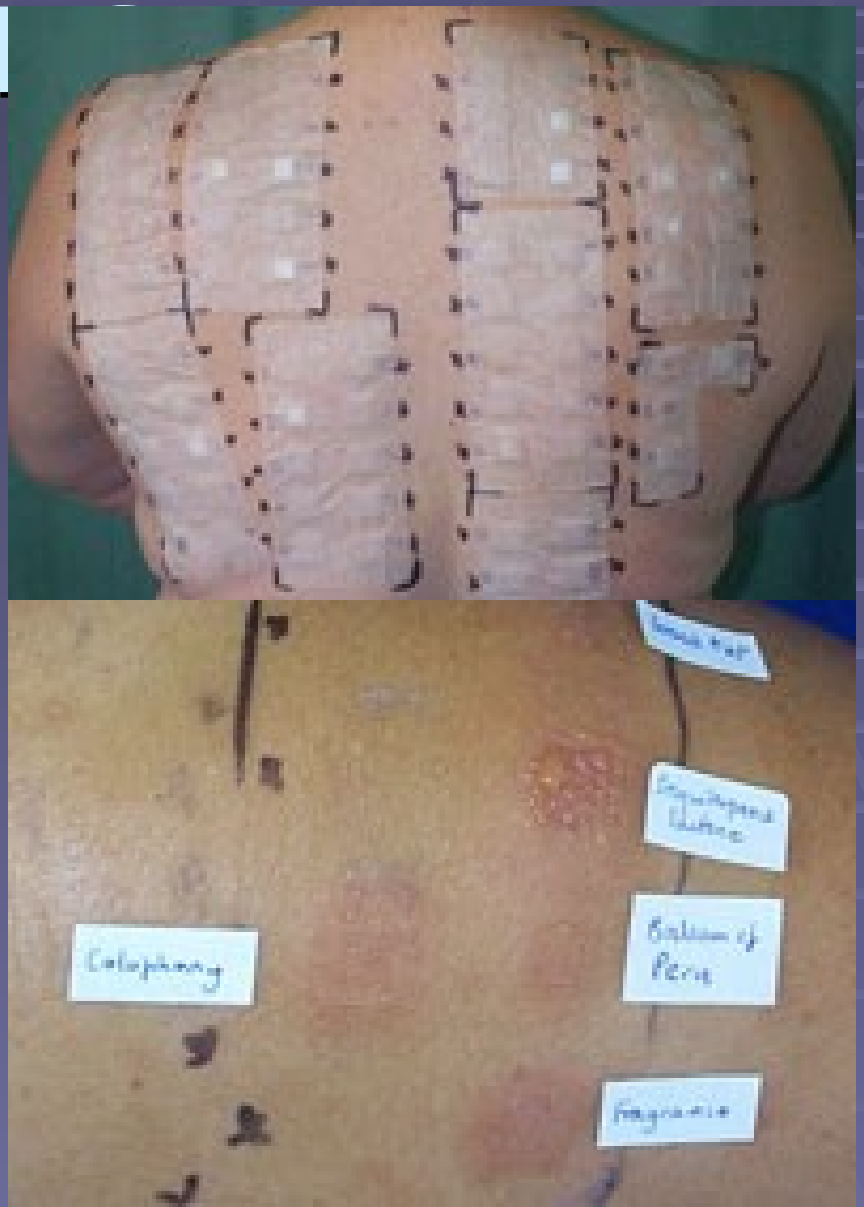


ARTHUS REACTION

- Local cutaneous vasculitis with necrosis due to immune complexes formed by circulating antibodies that bind to injected antigen in a previously immunized patient

TYPE IV HYPERSEI

- Diseases Caused by T Lymphocytes
  - Tissue injury from two mechanisms
    - Delayed-type hypersensitivity reactions (DTH)
      - T lymphocytes release cytokines that attract mononuclear cell infiltration
      - Lesions appear in 24-48 hours; Peak in 72 hrs
    - Directly killing target cells
  - DTH tissue injury mediators
    - Activated macrophages
      - Hydrolytic enzymes
      - Reactive oxygen intermediates
      - Nitric oxide
      - Proinflammatory cytokines



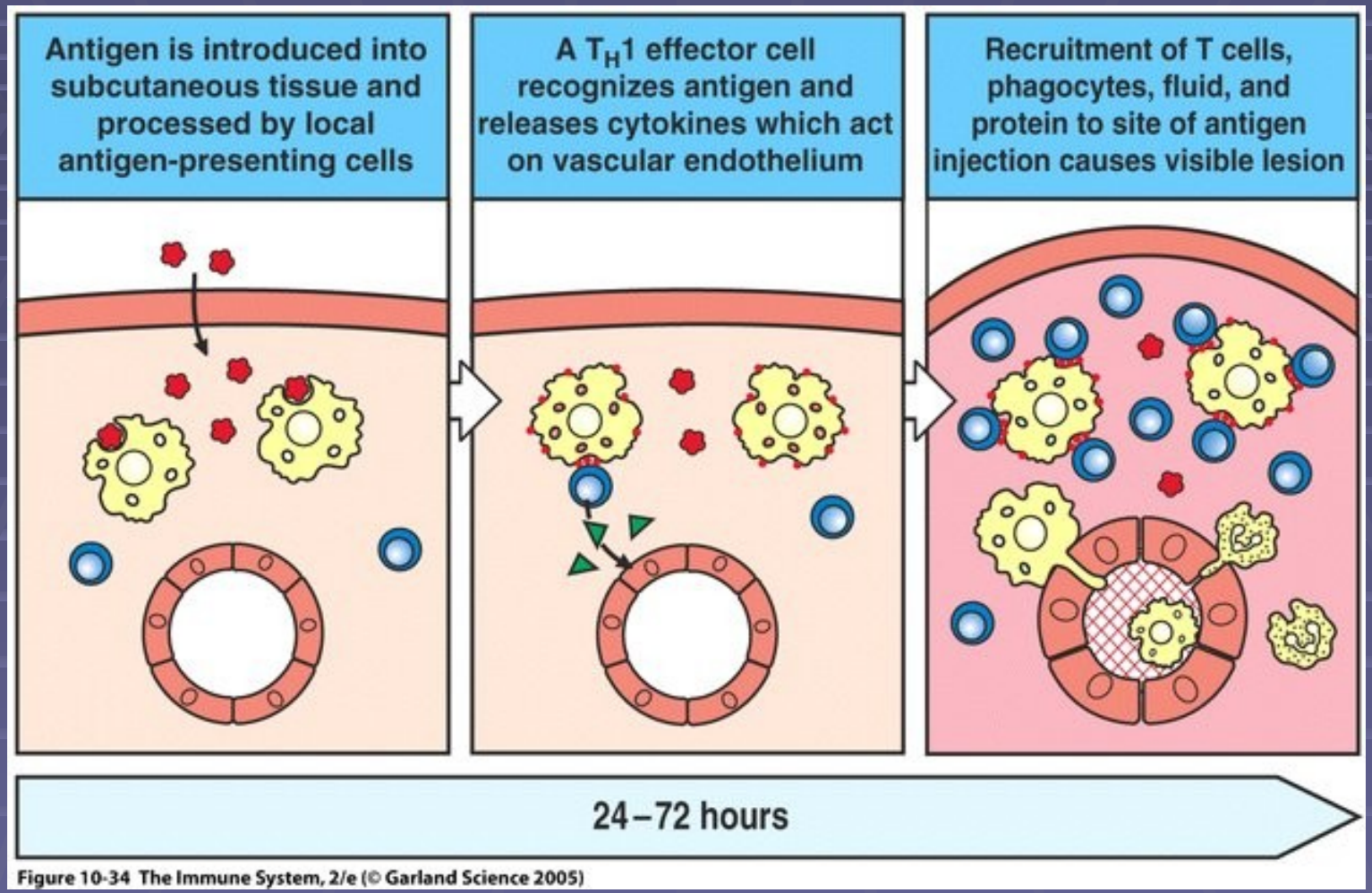

Antigen is introduced into subcutaneous tissue and processed by local antigen-presenting cells
A T_H1 effector cell recognizes antigen and releases cytokines which act on vascular endothelium
Recruitment of T cells, phagocytes, fluid, and protein to site of antigen injection causes visible lesion
24–72 hours

Figure 10-34 The Immune System, 2/e (© Garland Science 2005)

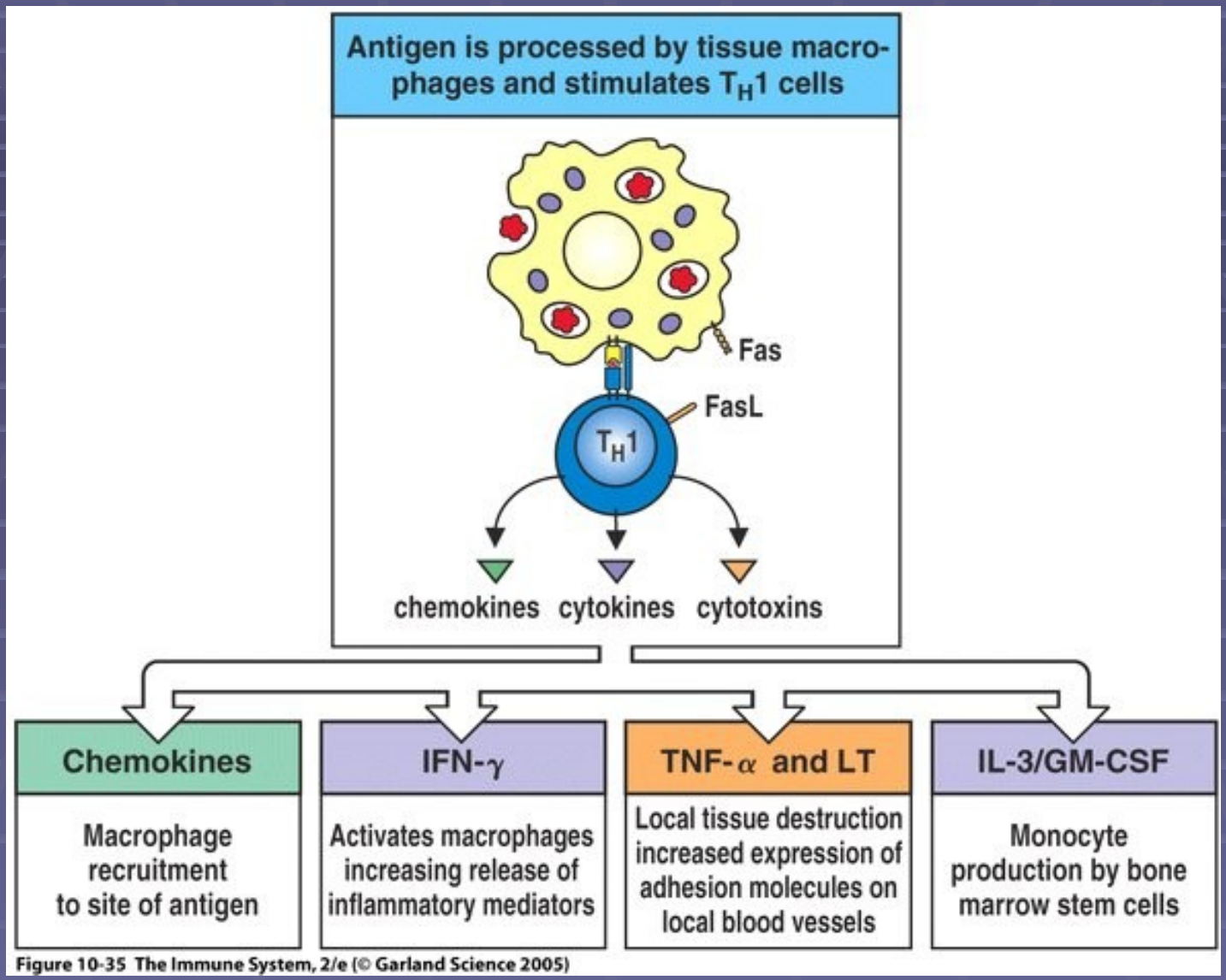


Figure 10-35 The Immune System, 2/e (© Garland Science 2005)

SUMMARY

	Time	Mediators	Examples
Type 1	2-30 minutes	IgE causes immediate mast cell degranulation	Local or systemic anaphylaxis Food or milk allergies
Type 2	Hours to a day	IgG or IgM antibody mediated cytotoxic (lysis or phagocytosis)	Blood transfusions Myasthenia gravis
Type 3	Hours to days	IgG or IgM antibody:antigen complexes cause complement activation	Serum Sickness
Type 4	24-72 hours	T cell mediated	Allergic Contact Dermatitis

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